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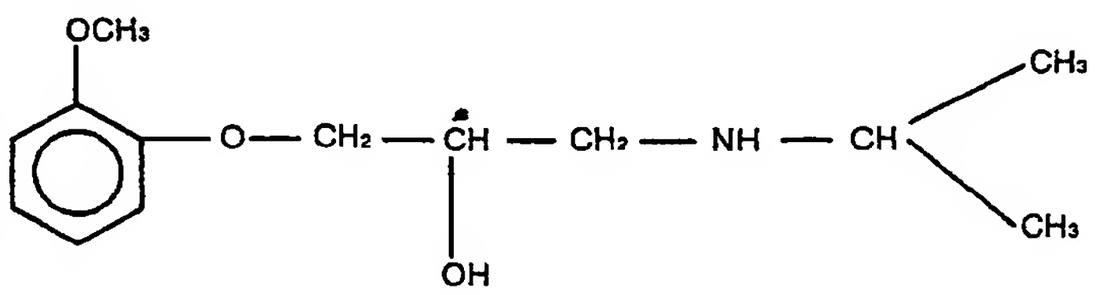
(54) Process for the separation of the two optical isomers of 1-(o-methoxyphenoxy)-3-isopropylamino-propan-2-ol, optical isomers obtained thereby and pharmaceutical compositions of the levorotatory antipode thereof.

(57) A process for the separation of moprolol having formula (I) into its two optical antipodes, by salifying racemic moprolol with L(+)glutamic acid; treating the thus obtained mixture of diastereoisomeric salts with a water/alcohol mixture, in this way separating the L(+)glutamate insoluble salt of (+)moprolol; treating the resultant mother liquors which contain in solution the L(+)glutamate salt of (−)moprolol with a base so as to separate the levorotatory isomer of crystalline moprolol, which finally undergoes a purification.

Also a pharmaceutical composition containing said levorotatory isomer of moprolol.



(I)

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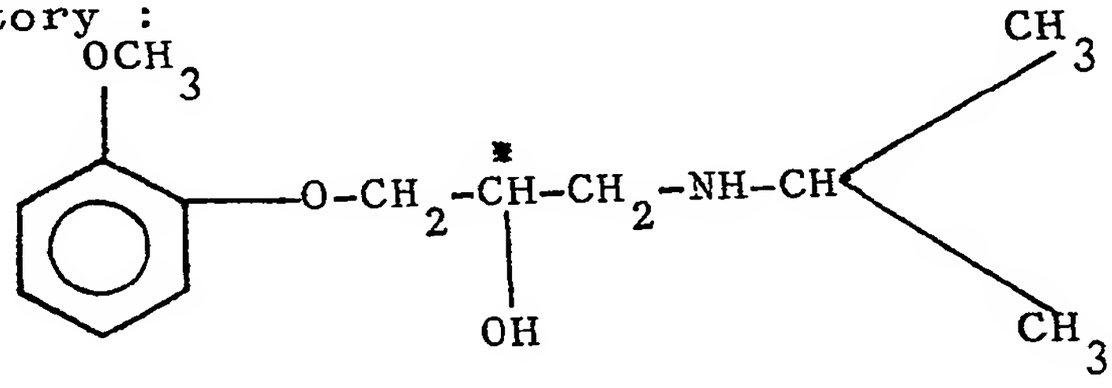
Process for the separation of the two optical isomers of moprolol and pharmaceutical compositions of the levorotatory antipode thereof . -

The present invention relates to a novel method of separation of racemic moprolol into its optical antipodes, of which latter a physico-chemical characterization is furthermore given, and to the corresponding pharmaceutical compositions which contain the pure levorotatory isomer, of which a pharmacological spectrum has also been defined in comparison with the racemic form and the dextro-rotatory antipode.

Moprolol, which is chemically 1-(o-methoxy-phenoxy)-3-isopropyl-amino-propane-2-ol (U.S. Patent No.3 911 136) is a β -blocking agent which is endowed with outstanding pharmacological properties. It is a racemic compound which has an asymmetric carbon atom in its basic side chain, such atom being marked by an asterisk in formula (I) and giving rise to the possibility of having two optical antipodes, the levorotatory and the dextro-rotatory :



(I)

β-blocking agents, generally speaking, are a class of chemical compounds of outstanding pharmacological and clinical importance (Ann.Rep.Med. Chemistry, 10, 51, 1975).

Their employment in human therapy includes the treatment of cardiac diseases (angina pectoris, myocardial infarction, arrhythmia), vascular diseases (hypertension), psychic illnesses (anxiety, essential tremor, schizophrenia).

It is well known that the pharmacological activity of such types of substances is directly correlated with their β-blocking activity, that is their ability to block the β-receptors, by occuping them instead of the physiological adrenergic amines, in all those pharmacological or pathological cases characterized by an excess of adrenergic activity.

It is also known (Nature, 210, 1335, 1966; Il Farmaco Ed. Sc. 21, 299, 1966) that the β-blocking activity of such substances is generally entirely ascribable to the levorotatory form of said substances while the dextro-rotatory form seems to be devoid of activity, or at least to be of very low activity.

It is, finally, known that in human therapy the β-blocking agents should be administered in sufficient dosages and amounts to maintain the β-block for 24 hours, and that such treatment should be prolonged for extended periods of time. Hence it follows that toxic side effects may appear such as cardiotoxicity, which is ascribable to an aspecific depressant action on the myocardial membrane, and bronchial constriction.

The maintaining of an unchanged activity and at

the same time halving the therapeutical dose of such drugs and subsequently greatly reducing the toxicological effects would be a cause of real clinical progress.

A first aim of the present invention is therefore to provide a method for the separation of the optical antipodes of moprolol such as to obtain the dextrorotatory and the levorotatory isomer with an elevated degree of optical purity.

A further aim of the invention is the preparation of moprolol-based compositions characterized by a β-adrenergic receptor blocking activity, such as call for a therapeutic dose of active ingredient that is very considerably lower than that of compositions of racemic moprolol, in this way greatly reducing any possible toxicological risk resulting as side effect of prolonged administration thereof.

In this regard it has now been surprisingly found, and this represents one of the aspects of the present invention, that the activity of the levorotatory isomer of moprolol is exactly double that of racemic moprolol, while the activity of the dextro-rotatory isomer is practically nil. From this it follows, for the reasons heretofore set out, that the clinical use of levorotatory moprolol would make possible dosages half as large as those required for the racemic form, with identical therapeutic effect and obviously with fewer toxicological effects. This is particularly advantageous in the therapeutic treatment of certain diseases which draw evident advantage from treatments with β-blocking drugs, which are however necessary in continued and high doses. Particular reference is made to hyperten-

sion, angina pectoris and certain types of anxiety state.

To achieve the aims described above, the present invention proposes a process for the separation of moprolol into its two optical antipodes, such process being substantially characterized by the salification of racemic moprolol with L(+) glutamic acid; by treating the thus obtained mixture of diastereoisomeric salts with a water/alcohol mixture, in this way separating the L(+) glutamate salt of crystalline (+)moprolol; by treating the resultant mother liquors, after their purification, with a base in aqueous solution to give (-) moprolol base, which is finally purified to a high degree of optical purity.

A preferred process according to the invention provides for salifying the racemic moprolol with an equimolecular quantity of L(+)-glutamic acid in an alcohol/water mixture and, after solvent evaporation, obtaining the mixture of the two optically active salts. This mixture is treated with an appropriate quantity of isopropanol/methanol/water in the ratio 80/15/5 and yields a crystalline solid consisting of the practically pure L(+) glutamic (+) moprolol salt. The mother liquors of crystallization, brought to dryness and taken up with a mixture of IsOH/MeOH in a 95/5 ratio, yield after filtration of the insoluble portion a solution containing the non-crystalline L(+)glutamic(-)moprolol salt practically alone, this salt being considerably more soluble in these solvents than the corresponding crystalline L(+)glutamic (+)moprolol salt.

By evaporation of the solvents there is obtained an oil which, after treatment with bases selected among

NH_4OH, $NaHCO_3$, Na_2CO_3, K_2CO_3, NaOH, KOH etc. in aqueous solution, provides the levorotatory isomer in crystalline form.

One recrystallization from ehtyl acetate gives a product with an optical purity $\geq$ 96%. A further optical purification is obtained by converting said 96% base into the corresponding hydrochloride with gaseous HCl in solvents selected among diethyl ether, acetone, ethyl acetate, or more conveniently by means of the following method which is suitable for preparation on industrial scale.

By dissolving an amount of base (5-10 kg) in 5-10 parts of chloroform and adding an equivalent amount of aqueous concentrated HCl, a solution is obtained which, when dried over Na_2SO_4 and evaporated to dryness under vacuum, gives the crystalline hydrochloride of (-) moprolol. A crystallization from absolute EtOH/EtOAc in the ratio 10/90, or EtOH 95°/EtOAc 5/95 gives rise to the levorotatory moprolol hydrochloride with an optical purity higher than 99%, which does not increase after subsequent and repeated crystallizations. The same operations applied to L(+)moprolol(+)glutamate gives the dextro-rotatory isomer of moprolol with an optical purity which is again $>$ 99%. The specific optical rotation of the two antipodes are respectively :

(-)moprolol hydrochloride $[\alpha]$ -16,8 $\pm$ 0,2 (c=5 absolute EtOH)

(+)moprolol hydrochloride $[\alpha]$ + 17,0 $\pm$ 0,2 (c=5 absolute EtOH)

Thus, in broad outline, the process for the separation of the optical antipodes of moprolol according to the invention is carried out by employing (+)glutamic

acid. In fact, it has been found that moprolol glutamate can be easily separated by crystallization into its antipodes; L(+)moprolol(+)glutamate and L(-)moprolol (+) glutamate.

The salt containing the levorotatory antipode is the more soluble and therefore it remains in the mother liquors from which the dextro-rotatory antipode has separated in the solid state. By evaporating the solvent the levorotatory antipode is obtained as a salt of glutamic acid. The levorotatory base, in its turn, is obtained by removing the salt according to known methods. The levorotatory isomer is finally crystallized from a solvent such as ethyl acetate. Subsequently the base is converted into hydrochloride, inasmuch as the levorotatory base obtained from the hydrochloride possesses an absolute optical purity.

In order better to describe the method according to the present invention, examples of realization are reported below which in any case is not to be considered as limiting the scope of the invention.

EXAMPLE 1

9.45 kg of racemic moprolol base, dissolved in 20 litres of methanol, were added to a suspension of 6 kg of L(+)glutamic acid $[\alpha]$= + 29 (c= 1 HCl 6N) in 16.5 litres of H_2O. The mixture was stirred at 50°C to complete dissolution, then concentrated to dryness in vacuo. The semi-solid residue was dissolved in 20 litres of methanol/water 3/1, then diluted with 80 litres of isopropanol. The whole was left at 4°C, after which 7.8 kg of L(+)moprolol(+)glutamate salt crystallized which was then filtered off. The mother liquors were then again concentra-

ted to dryness and the residue was treated with 10 litres of isopropanol/methanol 95/5. The insoluble portion (0.5 kg) was filtered off and the filtrate was concentrated to dryness; the residue was dissolved in 15 litres of H_2O, cooled to 0°C and treated with 40% NaOH to pH 12. The crystallized solid formed by (-)moprolol base, after a suitable period in a refrigerator was centrifuged, washed with water and dried to constant weight : 4.3 kg $[\alpha]_D$ -4° ± 0,2 (c= 5 absolute ethanol).

By crystallization from ethyl acetate, 3.5 kg of levorotatory moprolol were obtained, m.p. 78-80°C $[\alpha]_D$ = -5,5 ± 0,2 (c = 5 EtOH). The crystallized product (3.5 kg) was dissolved in 15 litres of chloroform and treated under stirring with 1,28 litres of 36% HCl. The water was separated and then 2,5 kg of Na_2SO_4 were added, then it was filtered and concentrated to dryness. The solid residue was crystallized from 28 litres of ethyl acetate/ 95° EtOH 9/1 thus obtaining 3,8 kg of (-)moprolol hydrochloride, m.p. 124-125°C $[\alpha]_D$ -16,8 + 0,2 (c = 5 absolute EtOH).

8.3 kg of (+)moprolol L(+)glutamate were twice crystallized from IsOH/MeOH/H_2O = 60/30/10 thus obtaining 6.6 kg of the salt, m.p. 173-174°C $[\alpha]_D$ + 7 (c = 1,MeOH). A suspension of 6.5 kg of salt in 20 litres of water and 10 litres of chloroform was alkalinized at 10°C with 40% NaOH. The organic phase was separated, washed with water, dried and concentrated. The solid residue after crystallization from ethyl acetate gave 3.25 kg of (+)moprolol, m.p. 78-80°C $[\alpha]_D$ = 5,75 ± 0,2 (c = 5 absolute EtOH). Such product, converted to hydrochloride and crystallized from ehtyl acetate/ethyl alcohol as for the correspond-

ing levorotatory isomer, gave rise to a producy of the following characteristics : m.p. 124-125°C $[\alpha]$= 17,0 ± 0,2 (c = 5 absolute EtOH).

A further aspect of the present invention is to provide for pharmaceutical compositions, particularly active as β-adrenergic receptor blocking agents, characterized by the fact of containing as active principle the pure levorotatory antipode of moprolol.

The (-)moprolol base can be converted into an acceptable salt for therapeutical employment by treatment according to known methods with inorganic or organic salts which are suitable for such preparations. (-)moprolol hydrochloride ($C_{13}H_{21}NO_3$.HCl) has m.p. 124-125°C.

For a therapeutical employment, (-)moprolol hydrochloride can be formulated as tablets, sugar- or film-coated tablets, beads, solutions for drops, vials, suppositories, eye salve, hard or soft gelatin capsules, both long-acting and normal-acting, in single doses of from 5 to 250 mg.

The dosage forms realized according to pharmaceutical techniques are produced with the aid of suitable known excipients or accessories.

In this regard, description is given below of two examples of realization of pharmaceutical dosage forms according to the invention, which are not however to be considered limiting.

EXAMPLE 2

A mixture of 375 g of levorotatory moprolol hydrochloride, 775 g of starch, 1200 g of microcrystalline cellulose and 100 g of talc was sieved, then carefully mixed with 800 ml of double distilled water. The resultant mix-

ture was granulated, then oven-dried for 12 hours at 50°C. After sieving through a narrow-mesh screen, the dry granulate had magnesium stearate (2% over total weight) added to it, was thoroughly blended and compressed into 500 mg tablets, each containing 75 mg of active ingredient.

EXAMPLE 3

15 g of levorotatory moprolol hydrochloride was separately dissolved in approximately 2 litres of double distilled water, and 48 g of sodium chloride in approximately 2 litres of double distilled water. The two solutions were combined and 60 ml of Esteril 10% was slowly added to them under stirring. The whole was then made to 6000 ml with dcuble distilled water and aseptically filtered. The filtered solution was filled under an atmosphere of nitrogen into yellow-glass vials in the measure of 2 ml each. Each vial thus contained 5 ml of active ingredient. The vials were then sterilized in autoclave for 30 minutes at 110°C.

In order better to clarify the advantages connected with the use of pharmaceutical compositions according to the present invention, the attached drawings include three diagrams relating to certain experiments conducted in anesthetized dogs. These diagrams concern the inhibition by racemic moprolol, its levorotatory optical isomer and its dextro-rotatory optical isomer, of certain homodynamic effects due to stimulation of the adrenergic β -receptors following on intravenous infusion of isoproterenol at a dose of 0.25 µg/kg/minute.

Figure 1 shows the increase in heart rate due to administration of isoproterenol at the aforesaid dose,

after duodenal administration of racemic moprolol (dotted line curve) at a dose of 0.5 mg/kg, of levorotatory moprolol (continuous curve) at a dose of 0.25 mg/kg and of dextro-rotatory moprolol (dashed line curve) at a dose of 0.25 mg/kg.

Similarly, diagram of FIG. 2 shows the increase of the hemodynamic parameter $\frac{dP}{dt}$ and diagram of FIG. 3 shows the decrease of diastolic arterial pressure, again after administration of isoproterenol at the above-identified dose and after administration of racemic moprolol and its pure optical isomers according to the aforesaid doses. The curves therein reported refer to the means of the results of three tests for each substance.

As can be seen by examining said diagrams, the inhibiting activity on the above-indicated hemodynamic effects, due to the stimulation of the β-adrenergic receptors effected by isoproterenol, is particularly evident for the levorotatory form in a dose-dependent manner, and with a highly significant correlation coefficient ($P < 0.01$) at the doses of 0.25, 0.0625 and 0.125 mg/kg of levorotatory moprolol.

As regards the administration of the racemic form of moprolol, nearly the same effects as indicated above, with the same significance, become evident at exactly doubled doses, namely 0.5 mg/kg, as can be seen from the diagrams, 0.125 and 0.25 mg/kg respectively.

There can also be seen from the attached diagrams the almost complete lack of β-blocking activity on the part of the dextro-rotatory optical isomer.

The observation made on the β-blocking activity possessed by levorotatory moprolol as compared with the

lack of activity of its dextro-rotatory isomer should not be seen separately from an evaluation of the toxicity of the said compounds. In this regard the following Table reports the LD_{50} of the single isomers and of the racemic product.

TABLE I

Compound	Lethal Dose$_{50}$ (LD_{50}) in the mouse
Moprolol (±)	712 mg/kg weight animal
Moprolol (-)	605 mg/kg weight animal
Moprolol (+)	720 mg/kg weight animal

The data given in Table I evidence similar toxicity of the three different compounds. However, and as is known, for an exact evaluation of the activity of a drug its intrinsic toxicity has to be seen in relation to the activity demonstrated, i.e. the median effective dose (ED_{50}).

In this regard the following Table II gives the respective data for the three compounds (±); (-); (+).

TABLE II

Compound	Median Effective Dose (ED_{50}) dog
Moprolol (±)	0.150 mg/kg weight animal
Moprolol (-)	0.0781 mg/kg weight animal
Moprolol (+)	n i l

The data given above very clearly express the relationship existing between the doses employed, which demonstrate the activity of levorotatory moprolol as compared with the racemic and dextro-rotatory forms.

There is no doubt that the most advantageous effective dose is the one relating to levorotatory moprolol

(0.0781 mg/kg weight animal), whereas to obtain the same response with the racemic product 0.150 mg/kg weight animal is required.

The dextro-rotatory moprolol shows the same toxicity as the levorotatory isomer and the racemic form, but without any activity whatsoever. It therefore appears evident that the effective dose of levorotatory moprolol is 2 times more active, inasmuch as it is 2 times smaller, than that expressed by the racemic form.

It is thus clear that the pharmaceutical compositions based on levorotatory moprolol proposed by the present invention make it possible advantageously to achieve the purpose, initially set, of accompanying an elevated β-blocking activity by a considerable reduction of the risk of toxicological effect which might derive from a prolonged administration.

C L A I M S :

1. Process for the separation of moprolol into its two optical antipodes, substantially characterized by the fact of salifying racemic moprolol with L(+)glutamic acid; treating the thus obtained mixture of diastereoisomeric salts with a water/alcohol mixture, in this way separating the L(+)glutamate insoluble salt of (+) moprolol; treating the resultant mother liquors which contain in solution the L(+)glutamate salt of (-)moprolol with a base so as to separate the levorotatory isomer of crystalline moprolol, which finally undergoes a purification.

2. A process according to claim 1, characterized by the fact that said racemic moprolol and said L(+)glutamic acid are reacted in a ratio of substantially 1 : 1.

3. A process according to claim 1, characterized by the fact that said water/alcohol mixture is isopropanol/methanol/water.

4. A process according to claim 2, characterized by the fact that said mixture is isopropanol, methanol and water in a ratio of substantially 80/15/5 by volume.

5. A process according to claim 1, characterized by the fact that said mother liquors which come from the separation of the insoluble dextro-rotatory isomer undergo a purification before being treated with a base.

6. A process according to claim 5, characterized by the fact that said purification of the mother liquors is carried out by drying the same, then taking them up with an alcoholic mixture, preferably isopropanol/methanol in the ratio 95 : 5, and filtering the thus obtained insoluble residue.

7. A process according to claim 1, characterized by the fact that said step of separating the levorotatory isomer of moprolol is carried out by treating said mother liquors with an aqueous solution of a base which is preferably selected from among : soda, sodium bicarbonate, sodium carbonate, potassium carbonate, ammonia, potassium hydroxide.

8. A process according to claim 1, characterized by the fact that said treatment of final purification comprises a recrystallization of the levorotatory isomer from ethyl acetate, to give a product with an optical purity $> 96\%$.

9. A process according to claim 8, characterized by the fact that said recrystallized levorotatory isomer with an optical purity $> 96\%$ is converted into the corresponding hydrochloride by treatment with gaseous HCl in an organic solvent solution, preferably ethyl ether, acetone, or ethyl acetate.

10. A process according to claim 8, characterized by the fact that said recrystallized levorotatory isomer, with an optical purity $> 96\%$, undergoes a further treatment of purification including the steps of dissolving in chloroform, adding concentrated aqueous HCl to give a solution, drying with Na_2SO_4, finally evaporating to dryness in vacuo to give crystalline (-)moprolol hydrochlo-

ride, recrystallizing this latter from a mixture ethanol/ethyl acetate to give the levorotatory moprolol hydrochloride with an optical purity $> 99\%$.

11. A process according to claim 10, characterized by the fact that said mixture ethanol/ethyl acetate is in the ratio 10 : 90 respectively, absolute ethanol being utilized.

12. A process according to claim 10,characterized by the fact that said mixture ethanol/ethyl acetate is in a ratio 5 : 95, 95° ethanol being utilized.

13. A process according to claim 1,characterized by the fact that said L(+)glutamate salt of (+)moprolol, which is separated in the crystalline state, is subsequently treated so as to give the pure dextro-rotatory isomer of moprolol.

14. The levorotatory isomer of moprolol, and the hydrochloride thereof, when obtained by a process according to any one of the preceding claims.

15. The dextro-rotatory isomer of moprolol, and the hydrochloride thereof, when obtained by a process according to any one of claims 1 to 13.

16. The levorotatory isomer of moprolol and pharmaceutically acceptable salts thereof when obtained by a process substantially as described in Example I.

17. A pharmaceutical composition comprising the levorotatory isomer of moprolol claimed in claim 14 or 16 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient.

18. A pharmaceutical composition comprising a pharmaceutically acceptable salt of the levorotatory isomer of moprolol, in unit dosage form in which each unit contains

between 5 and 250 mg of the moprolol salt.

19. A composition according to claim 18 which also contains a pharmaceutically acceptable excipient.

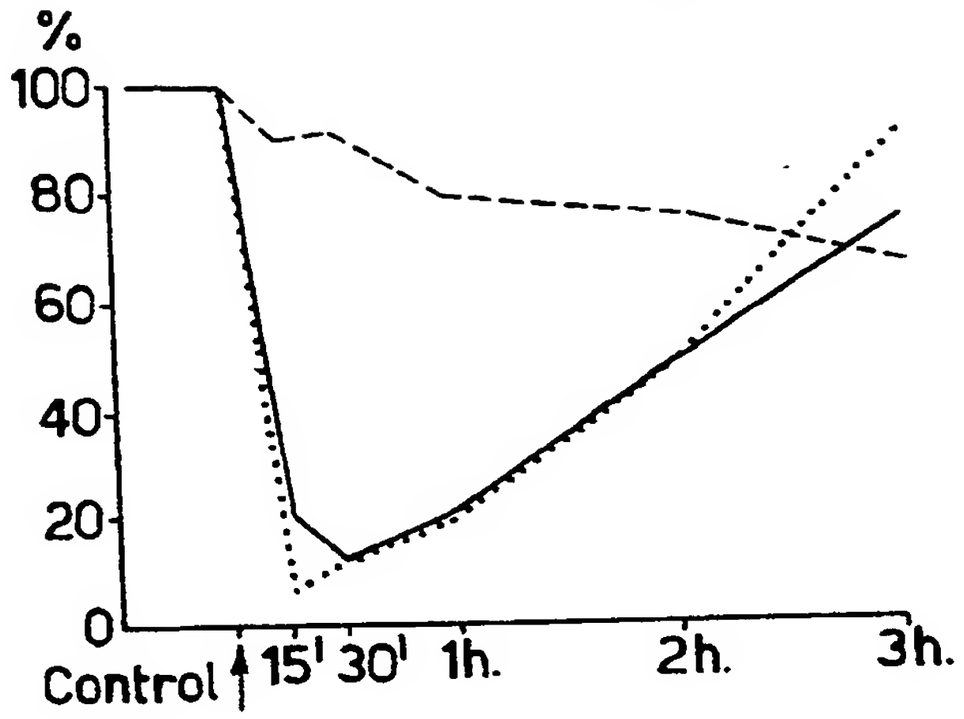


Fig.1

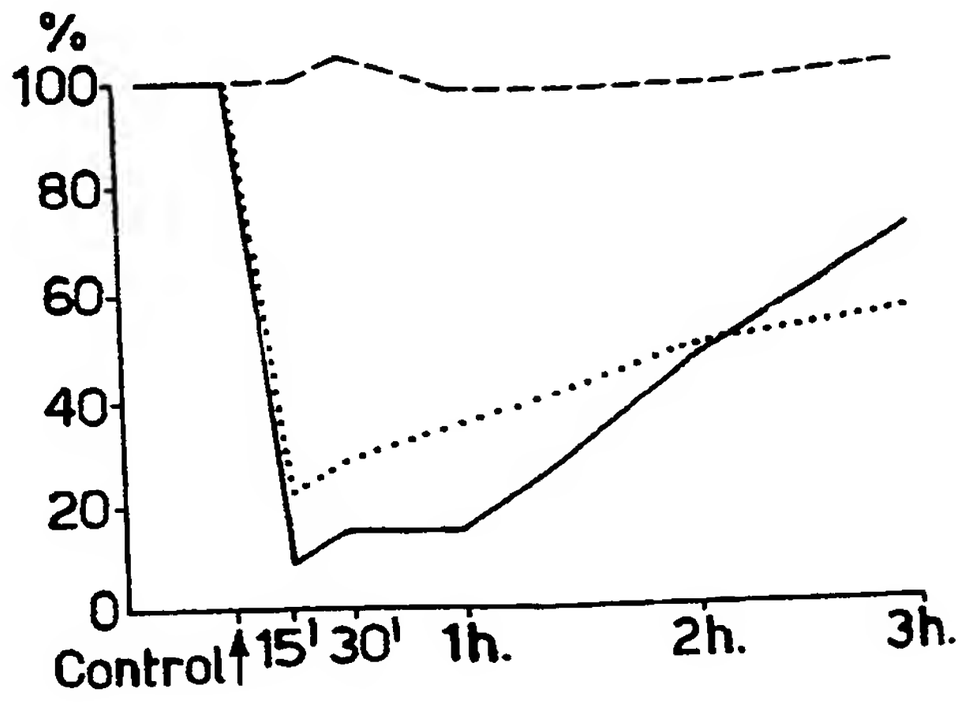


Fig.2

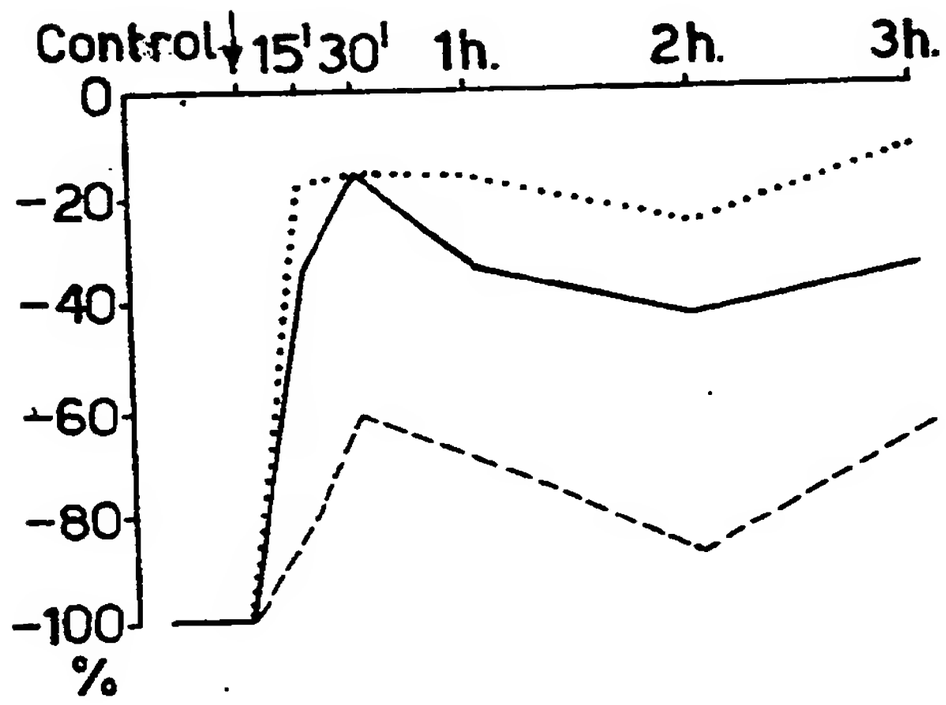


Fig.3

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	ARZNEIMITTEL-FORSCHUNG, vol. 20, no. 8, August 1970 Aulendorf, DE R. FERRINI et al. "Pharmacological Actions of 1-(0-Methoxyphenoxy)-3-isopropylamino-2-propanol Hydrochloride (S-D/1601), a New β-Blocking Agent", pages 1074-1079. * Whole paper * --	1, 14-19	C 07 B 19/00 C 07 C 93/06 A 61 K 31/135
	US - A - 3 432 545 (R. HOWE) * Whole patent * ----	1-19	

TECHNICAL FIELDS SEARCHED (Int.Cl.)

C 07 B 19/00
C 07 C 93/06

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	28-05-1980	ALLARD

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